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Fecal Calprotectin Level in Patients with Rosacea: Gut Inflammation May Be Associated with the Type of Rosacea, A Case-Control Study

Rozasea Hastalarında Fekal Kalprotektin Düzeyi: Bağırsak İltihabı Rozasea Tipi ile İlişkili Olabilir, Bir Vaka-Kontrol Çalışması

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ABSTRACT Objective: Rosacea is a chronic inflammatory skin disease that has complex pathogenesis. The association between rosacea and inflammatory gastrointestinal tract disorders is a popular topic, and fecal calprotectin is a potential marker to diagnose intestinal inflammation of any cause. In this study, the aims were to determine the relationship between disease type, disease severity, and fecal calprotectin levels in patients with rosacea, and also compare the calprotectin levels between healthy controls and rosacea patients. **Material and Methods:** Forty-six patients with rosacea, and sex-age-matched 92 healthy volunteers were enrolled in this study. Calprotectin levels of stool samples were calculated using enzyme-linked immunosorbent assay. **Results:** Of these patients, 30 (65.2%) had erythematotelangiectatic type rosacea, and 16 (34.8%) had papulopustular type rosacea. There was not a statistically significant difference between the mean fecal calprotectin levels of the patient and control groups (p=0.414), whereas the mean fecal calprotectin levels of the erythematotelangiectatic type group was lower than the papulopustular type group, and this difference was significant (p<0.001). **Conclusion:** According to the results, the underlying pathogenesis of different types of rosacea may be different, and the papulopustular type of rosacea may be more related to gut inflammation. In addition, we think that fecal calprotectin may be useful in evaluating intestinal inflammation especially in patients with papulopustular type and severe rosacea.

Keywords: Rosacea; gastrointestinal tract; inflammation

ÖZET Amaç: Rozasea, karmaşık patogenezi olan kronik inflamatuar bir deri hastalığıdır. Rozasea ve inflamatuar gastrointestinal sistem bozuklukları arasındaki ilişki popüler bir konudur ve fekal kalprotektin, herhangi bir nedene bağlı intestinal inflamasyonu teşhis etmek için kullanılan potansiyel bir belirteçtir. Bu çalışmada, rozasealı hastalarda hastalık tipi, hastalık şiddeti ile fekal kalprotektin düzeyleri arasındaki ilişkiyi ve sağlıklı kontrollerle farkını belirlemek amaçlandı. **Gereç ve Yöntemler:** Bu çalışmaya rozasealı 46 hasta ve cinsiyet-yaş uyumlu 92 sağlıklı gönüllü alındı. Dışkı örneklerinin kalprotektin seviyeleri, enzime bağlı immünosorbent tahlili kullanılarak hesaplandı. **Bulgular:** Bu hastaların 30'unda (%65,2) eritematotelanjiektatik tip rozasea, 16'sında (%34,8) papülopüstüler tip rozasea vardı. Hasta ve kontrol gruplarının ortalama fekal kalprotektin düzeyleri arasında istatistiksel olarak anlamlı fark bulunmazken (p=0,414); eritematotelanjiektatik tip hastalığı olan grubun ortalama fekal kalprotektin düzeyleri papülopüstüler tip grubuna göre daha düşüktü ve bu fark anlamlıydı (p<0.001). **Sonuç:** Elde edilen sonuçlara göre farklı rozasea türlerinin altta yatan patogenezi farklı olabilir ve papülopüstüler tip rozasea daha çok bağırsak iltihabı ile ilişkili olabilir. Ayrıca özellikle papülopüstüler tip ve şiddetli rozasealı hastalarda, fekal kalprotektinin intestinal inflamasyonun değerlendirilmesinde faydalı olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Rozasea; gastrointestinal kanal; inflamasyon

Rosacea is a chronic dermatological disorder that mostly affects light-skinned people in the world. It is characterized by recurrent episodes of flushing which finally leads to chronic erythema and telangiectasia, also other skin conditions as papules, pustules, sebaceous hyperplasia, and some ophthalmologic symp-

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toms.[1,2] Rosacea negatively affects the lives of patients due to its cosmetic effects and symptoms.[3]

The exact etiopathogenesis of rosacea has not been elucidated. There is some evidence implicate that dysregulated production and secretion of inflammatory cytokines, abnormal neurovascular activation, and overgrowth of microorganisms that are normally found on the skin have roles in the pathogenesis of rosacea.[4] It was also shown that the underlying mechanisms of dermatological diseases are influenced not only by skin microbiota but also by gut microbiota.[2] Authors alleged that intestinal bacteria can activate the plasma kallikrein-kinin pathway which leads to burning, stinging, and flushing symptoms of rosacea due to the episodes of neurogenic inflammation.[5] Moreover, many studies reported a strong association between rosacea and inflammatory gastrointestinal (GI) tract disorders.[6,7]

Calprotectin is a member of the calcium-binding calgranulin protein family found in the neutrophils, with a proportion of 40-60% of the whole cytosolic proteins, and also found in macrophages, monocytes, and gut epithelial cells.[8] It can be measured in plasma, urine, and feces, and when there is inflammation, concentration of calprotectin is expected to increase.[9] Authors claimed that fecal calprotectin shows the neutrophil inflammation level in the gut and, can be a useful marker to discriminate inflammatory bowel diseases (IBD) from irritable bowel syndrome (IBS). Moreover, it has the potential to serve as a screening test to diagnose intestinal inflammation of any cause.[10]

To the best of our knowledge, there is only one study about fecal calprotectin levels in patients with rosacea.[11] The present study was conducted to investigate possible associations between rosacea and the gut further. Thus, fecal calprotectin levels were compared between rosacea patients and healthy controls, also evaluated according to disease severity, the subtype of rosacea, and more variables among the patient group.

MATERIAL AND METHODS

Study population: Patients with rosacea, aged over 18-under 65, presenting to the Dermatology Outpatient Clinic of Süleyman Demirel University Hospital between January 2020 and January 2021, and sex-age-matched healthy controls were considered for this study. Patients with a history of cardiovascular or cerebrovascular events, active gut symptoms (dyspepsia, constipation, diarrhea), active infection and systemic diseases (diabetes mellitus, hypertension, etc.) or skin diseases other than rosacea, and regular drug intake for any reason were excluded. But participants who have smoking and/or alcohol drinking habits (except excessive intakes) were not excluded. Also, antibiotic or probiotic use in the last month was questioned and these patients were excluded or postponed at least one month. The participants were also checked for a history of colonoscopies, or diagnoses of IBD and IBS.

Detailed medical histories of patients were taken, and skin examinations were performed. Two common types of rosacea (erythematotelangiectatic and papulopustular types) according to the National Rosacea Society Expert Committee were noted.[12] There has been no included patients with other rare types (phymatous and/or ocular) of rosacea in this study.

The severity of rosacea symptoms was assessed by Rosacea Clinical Scorecard on a 4-point scale where absent means 0, mild does 1, moderate does 2, and severe means 3 points. The Physician's Global Assessment and patient's global assessment are also 4-point scales.[13] According to these scales, patients were subdivided into 3 categories, and evaluation was done considering this subdivision: patients with mild, moderate, or severe disease.

Stool samples: Stool samples were collected from all participants and were stored at -80 ºC until analysis. After thawing of the samples, extraction, homogenization, and dilution steps were performed manually following the kit protocol. The fecal calprotectin levels were determined by using an available enzyme-linked immunosorbent assay (ELISA) kit (Ridascreen Calprotectin, R-Biopharm AG, Darmstadt, Germany). The assay procedure was a quantitative sandwich ELISA technique using a microplate that was precoated with specific monoclonal antibodies. All steps of the ELISA (reagent dispensing, incubation, washing, reading, and calculating re-

sults) were performed using an automated ELISA analyzer (Triturus, Grifols, Barcelona, Spain). Optical density (absorbance) was measured spectrophotometrically at 450 nm. The calprotectin concentration in each sample was determined by plotting a standard curve based on the standard concentrations and their corresponding optical densities. The measured absorbance was proportional to the calprotectin concentration present in the sample. The fecal calprotectin levels were expressed in mg/kg.

STATISTICAL ANALYSES

Data were analyzed using SPSS v. 20 (SPSS Inc.-Chicago, Illinois, USA). The values of descriptives were presented as mean, standard deviation, median, min and max. For analysis of continuous variables across groups; first the distribution characteristics were examined with the Shapiro-Wilk test. It is used Mann-Whitney U or Kruskal-Wallis test according to the number of groups for non-parametric distributions and independent samples t-test for normal distributed 2 groups. Also, Spearman correlation analysis was performed for 2 continuous/scale type variables. In all analyses, the p-value of <0.05 means significant.

Ethics Committee Approval: This prospective case-control study was reviewed by the Ethics Committee of Süleyman Demirel University Faculty of Medicine Clinical Research and approved by the report of decision number 334 on 05.12.2019. This study protocol was consistent with the Declaration of Helsinki.

RESULTS

Forty-six patients with rosacea and 92 healthy controls who provided informed consent were included. 22.2% (n=10) of the patients were male and 77.8% (n=35) of the patients were female, whereas in the control group 23.3% (n=21) of the participants were male and, 76.7% (n=69) were female. The mean age of rosacea patients and healthy control subjects were 43.8±13.3 and 42.9±13.8 years, respectively. There was no significant difference seen between the groups according to age and gender (p=0.320, p=0.93, respectively). Of these patients, 30 (65.2%) had erythematotelangiectatic type rosacea, and 16 (34.8%) had papulopustular type rosacea. There have been no included patients with ocular and/or phymatous rosacea. Rosacea patients had higher body mass index (BMI) than the control group (26.2 kg/m^2 vs 24.9 kg/m^2), but the difference was not significant (p=0.129). Descriptive features of the participants were given in Table 1.

The mean of fecal calprotectin levels in the patient group was 25.32 (±31.01) whereas in the control group it was 20.50 (±19.50), and there was no significant difference seen between the 2 groups (p=0.414) (Table 2). Furthermore, the fecal calprotectin levels of the patients were also evaluated according to the subtype of rosacea (erythematotelangiectatic or papulopustular types), the severity of the disease (as mild, moderate, severe disease subgroups), gender, smoking, and alcohol habits. There

TABLE 1: Baseline characteristics of the study groups.

	Patient group (n=46)		Control group (n=92)	p value
	Erythematel. type† (n=30)	Papulopust. type‡ (n=16)		
Age, years	43.8±13.3		42.9±13.8	0.320
Female, n (%)	38 (82.6)		74 (80.4)	0.93
Male, n (%)	8 (17.4)		18 (19.6)	
BMI, kg/m^2 BMI, kg/m^2	26.2±4.64		24.9±4.41	0.129
Duration of disease, years	7±5.3 (1-20)	6.5±6.9 (1-25)		
Mild disease, n (%) Moderate disease, n (%) Severe disease, n (%)	15 (50) 15 (50)	6 (37.5) 6 (37.5) 4 (25)		
Smoking, n (%)	8 (17.4)		36 (39.1)	0.017
Use alcohol, n (%)	2 (4.35)		9 (9.78)	0.336

†Erythematelangiectatic type; ‡Papulopustular type; BMI: Body mass index.

TABLE 2: Comparison of fecal calprotectin levels between the study groups.

	Patient group (n=46)	Control group (n=92)	p value
Fecal calprotectin	25.32±31.01	20.50±19.50	0.414

was also no significant difference according to gender, age and BMI between erythematotelangiectatic or papulopustular type patients (p=0.694, p=0.296, and p=0.124 respectively) (Table 3). The mean fecal calprotectin levels of the papulopustular type group was higher than the erythematotelangiectatic type group-and there was a significant difference between the 2 groups (p<0.001) (Table 4, Figure 1). Interestingly, according to smoking habits, in the smoker group, the mean fecal calprotectin level was increased more with a significant difference (p=0.008) (Table 4, Figure 2).

When the fecal calprotectin levels were compared among patients according to gender, the severity of the disease (mild, moderate, and severe), and alcohol habits, again no significant difference was seen in terms of each of these variables (Table 4).

TABLE 3: Comparison of gender, age and BMI among the patient group.

	Disease subtype		
	Erythematel. type† (n=30)	Papulopust. type‡ (n=16)	p value
Female	24	14	0.694
Male	6	2	
Age (mean)	45.4±12.7	40.8±16.1	0.296
BMI (mean)	25.2±3.48	27.8±6.48	0.124

†Erythematelangiectatic type; ‡Papulopustular type; BMI: Body mass index

TABLE 4: Comparison of fecal calprotectin levels according to type and severity of disease, smoking habit, and gender among the patient group.

		Fecal calprotectin level				
	n	Mean	Median	Minimum	Maximum	p value
Type of the disease						
Erythematel. type	30	13.28±5.41	12.25	7.00	29.70	<0.001**
Papulopust. type	16	47.89±44.67	37.30	4.00	156.00	
Severity of the disease						
Mild	21	25.03±32.6	13.50	8.00	156.00	0.427
Moderate	21	23.10±30.9	15.60	4.00	152.00	
Severe	4	38.45±25.8	37.30	8.00	71.20	
Smoking habit						
Active smoker	8	10.53±2.74	10.10	8.00	15.60	0.008
Non-smoker	38	28.43±33.33	16.85	4.00	156.00	
Gender						
Female	38	26.53±32.84	15.20	4.00	156.00	0.400
Male	8	19.56±21.13	12.25	8.00	71.20	
Alcohol use						
Active drinker	2	10.70±2.12	10.70	9.20	12.20	0.010*
Non-drinking	44	25.98±31.56	14.40	4.00	156.00	

*: p<0.05, **: p<0.001.

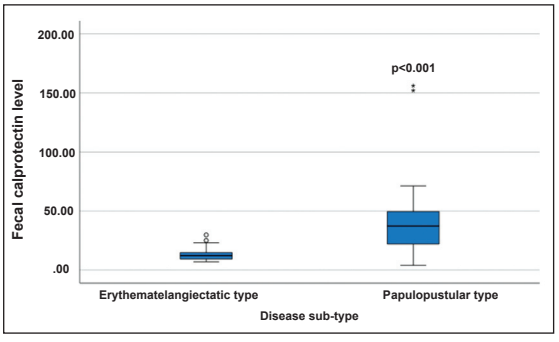

FIGURE 1: Comparison of fecal calprotectin levels according to the type of disease.

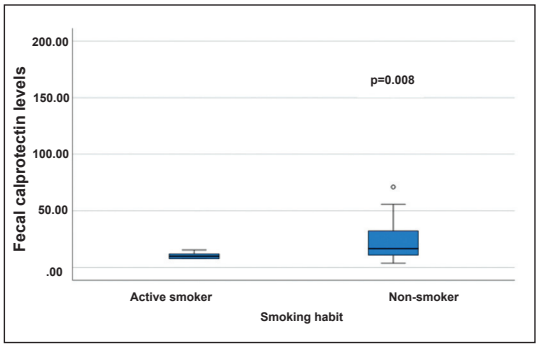

FIGURE 2: Comparison of fecal calprotectin levels according to smoking habit in the patient group.

DISCUSSION

We stated that the level of fecal calprotectin was significantly higher in the patients with papulopustular type rosacea than those with erythematelangiectatic type rosacea. Even though no statistically significant difference was shown between the fecal calprotectin levels of the patient group and the control group, these results may show us there could be different mechanisms in the pathogenesis of subtypes of rosacea, and the papulopustular type of rosacea may be more related to gut inflammation rather than the erythematelangiectatic type.

The exact underlying pathogenesis of rosacea has not been fully understood, but it is thought that rosacea results from multiple factors including genetic susceptibility, abnormal neurovascular signaling, the dysregulated immune system, and overgrowth of skin organisms.[3,14] Furthermore, alteration in the gut microbiome has also been blamed for the pathogenesis of rosacea and, a study revealed that certain bacteria were shown more abundant in patients with rosacea, whereas other bacteria populations were less than controls.[15] In that study, the results of patients were not classified according to the subtypes of rosacea, and the comparison was made only between healthy controls and patients. If classification was made according to the disease type, the presence of abundant bacteria may be found as associated with the rosacea type, especially with the papulopustular type, similar to our study.

Besides, a meta-analysis investigating common etiologic factors and conditions between rosacea and IBD showed that genetic susceptibility, alterations in innate and adaptive immunity, common risk factors such as obesity, smoking and, small intestinal bacterial overgrowth may be the shared factors in the etiopathogenesis of both diseases.[16] However, in this study, we found a significant difference between the fecal calprotectin levels of the 2 groups in terms of smoking habits. In the literature, we can see that the effects of smoking on the GI tract issue are contradictory. Some authors claimed that smoking may promote intestinal inflammation, can change the mucosal repair process in the gut and, might cause oversecretion of gastric acid and increases the probability of *Helicobacter pylori* infection and more; whereas some say that smoking is strongly associated with a lower incidence of ulcerative colitis.[17-19] Until now, no mechanism has been defined that can fully explain this contradictory situation. The promotion of gut inflammation by smoking may cause higher levels of fecal calprotectin levels in our healthy control group. For this reason, our results should be supported by future studies comparing smoker versus non-smoker patients and non-smoker healthy controls, as well.

In a cohort study of patients with rosacea, the prevalence of IBDs, celiac disease, small intestinal bacterial overgrowth, and *H. pylori* infection were found all higher among patients with rosacea as compared with healthy controls.[20] Likewise, Wu et al. reported that patients with rosacea may have an increased risk of having IBD.[7] Furthermore, Spoendlin et al. stated that patients with IBD may be more likely to develop rosacea particularly during phases of increased IBD-associated GI tract inflammation.[21] The results of all these studies observing the

association between rosacea and inflammation of the gut were compatible with the "skin-gut axis". This opinion proposed that GI dysbiosis affects the skin via immunologic, metabolic, and neurogenic pathways.[22] Moreover, a recent study by Yilmaz et al. reported that there may be a relationship between rosacea clinic and intestinal dysbiosis as a result of increased and decreased bacterial groups.[23] The reason we did not find a significant result on this subject between our study groups may be the low total number of patients and few patients with severe disease and, smoking may increase the fecal calprotectin levels especially in the control group.

In a recently published study by Aksu Çerman et al, fecal calprotectin levels were significantly higher in rosacea patients than in controls.[11] This study included 47 patients and 39 healthy controls, and evaluated GI symptoms between the 2 groups with the Gastrointestinal Symptom Rating Scale (GSRS), as well as fecal calprotectin. GSRS scores were also significantly higher in the patient group. According to the results of this study, unlike our results, they claimed that fecal calprotectin can be used for the evaluation and early detection of GI symptoms in patients with rosacea. Although the sample size in this study was smaller than ours, patients with rosacea had a more severe disease than ours, which may affect the results.

The concentration of fecal calprotectin was associated with infiltration of the intestinal mucosa by neutrophils. In addition, in IBDs, calprotectin was shown to be significantly correlated with clinical activity and also histopathological.[24,25] So, fecal calprotectin seems like a useful parameter in the diagnosis of the disease, estimation of relapse, and monitoring of IBDs.[24] Besides that, fecal calprotectin is an inflammatory marker that not only diagnostic for IBDs but also in inflammation-associated diseases.[26] It was evaluated in many dermatological diseases such as hidradenitis suppurativa (HS), Behçet's disease, psoriasis, scleroderma and atopic dermatitis.[27-32]

In a study from our country involving 50 patients with HS, patients with active disease had significantly higher fecal calprotectin levels compared to the patients with stable disease.[27] In addition, similar to our results, in that study, no significant difference was shown in fecal calprotectin levels between the patients and the healthy controls. In contrast, Kluger et al. did not show any higher fecal calprotectin levels in HS patients, even showing extra digestive symptoms.[28]

Adarsh et al. stated that fecal calprotectin level was high in 29 (58%) patients with psoriatic arthritis, 26 (26%) with psoriasis and three (10%) with IBS. Interestingly, sigmoid colonoscopies of 8 of these psoriasis patients with high fecal calprotectin levels revealed normal macroscopic findings even they had microscopic inflammation findings.[29]

Özşeker and et al. found significantly more elevated levels of fecal calprotectin in patients with Behçet's disease compared with controls.[31] They also showed that in patients who have GI involvement of Behçet's disease had higher fecal calprotectin levels compared to the patients without any GI involvement. Therefore, they reported that fecal calprotectin could be used as an important leading marker in the clinical evaluation of underlying GI inflammation even in cases without any symptoms.

In a recent study evaluating the possible predictive role of fecal calprotectin in small intestinal bacterial overgrowth diagnosis in patients with systemic sclerosis, they found more elevated fecal calprotectin levels in the patient group compared to healthy controls which were significant.[30]

In a study from South Korea, significantly elevated fecal calprotectin levels were seen in atopic dermatitis patients with severe disease than with mild disease and, they reported fecal calprotectin might be used to determine the clinical activity of atopic dermatitis in children.[9] In another study, Kim et. al showed that in murine models with induced atopic dermatitis, the fecal calprotectin levels decreased significantly after the administration of probiotics as well as attenuation of epidermal skin lesions. In the same way as previous studies, they reported that fecal calprotectin might be an essential marker to evaluate the inflammation of the gut.[32]

Our study is a cross-sectional study with relatively low number of participants. There should be an equal number of patients in each type of rosacea,

but in the present study, only patients with erythematelangiectatic and papulopustular types were included, not the ocular and/or phymatous types. Also, smoking was not an exclusion criterion in the selection of a healthy control group. Therefore, our results should be confirmed by future prospective studies with more participants.

CONCLUSION

The results of our study revealed that there could be different mechanisms in the pathogenesis of different types of rosacea, and the papulopustular type of rosacea may be more related to gut inflammation. There is only one study in the literature evaluating the fecal calprotectin level in rosacea.[11] As far as we know, this study is the second study on this subject. Our results revealed one more possible link between the especially papulopustular type of rosacea and gut inflammation even there was no significant difference between the patients and healthy controls. The treatment options of rosacea are limited, and some patients have a refractory condition to the conventional treatments. Increased understanding of the pathogenesis of rosacea will contribute to the development of novel therapeutics especially according to the subtype of the disease. Furthermore, as the relationship between rosacea and intestine shown in many previous studies is clarified, dietary modifications or recommendations which can reduce both symptoms and intestinal inflammation may become an absolute and the first base of the management of rosacea.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Havva Hilal Ayvaz, Mümtaz Cem Şirin;* ***Design:*** *Havva Hilal Ayvaz;* ***Control/Supervision:*** *Havva Hilal Ayvaz, Mümtaz Cem Şirin;* ***Data Collection and/or Processing:*** *Havva Hilal Ayvaz, Mümtaz Cem Şirin, Rahime Cankat Doğantekin;* ***Analysis and/or Interpretation:*** *Havva Hilal Ayvaz, Seda Atay;* ***Literature Review:*** *Havva Hilal Ayvaz, Seda Atay;* ***Writing the Article:*** *Havva Hilal Ayvaz;* ***Critical Review:*** *Selma Korkmaz, İjlal Erturan, Mehmet Yıldırım;* ***References and Fundings:*** *Havva Hilal Ayvaz, Seda Atay;* ***Materials:*** *Havva Hilal Ayvaz, Seda Atay.*

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